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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,185	11/21/2001	Krzysztof Palczewski	P-NS 4970	1224

7590 02/23/2004

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,185	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 30-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 10/30/03. The amendment has been entered. Claims 28, 29, 37 and 38 have been cancelled. Claims 1-26 and 30-36 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Specification

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code; for example, see page 7, line 30. Applicant is required to delete all embedded hyperlinks and/or other forms of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

4. Claims 1-27 and 30-36 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons of record.

Response to Arguments

5. Applicant's arguments filed 10/30/03 have been fully considered but they are not persuasive.

6. The claims are drawn to 1) a gene targeting construct or vector encoding a transgene having a rod outer segment (ROS) targeting signal flanked by homologous sequences to the mouse rhodopsin gene; and 2) a mouse cell or mouse whose genome is functionally disrupted at one or both endogenous rhodopsin gene alleles with the targeting construct.

7. It is noted that the gene targeting construct/vector and mouse cell have only been disclosed in the specification as being useful for making transgenic mice that express the gene of interest such that the protein encoded by the gene of interest is expressed and localized to the ROS of said transgenic mouse's eye. The specification indicates that the transgenic mice expressing the protein of interest can be used to isolate/purify the protein of interest (i.e., the mouse would be a bioreactor for producing the protein of interest), which could then be used to produce antibodies, or in crystallography experiments. Additionally, the specification indicates that the cells of the transgenic mouse can be used in drug screening assays (see p. 38 of the specification). However, in order to use the transgenic mouse (and thus the targeting construct/vector and mouse cell) as contemplated, the transgenic mouse MUST express the transgene of interest such that the protein encoded by the transgene is expressed in the ROS of the eye in amounts sufficient for purification or at a concentration sufficient for performing drug screening assays.

8. As previously indicated, the prior art indicates that it is unpredictable if a transgenic mouse comprising a transgene inserted into one or both rhodopsin genes (e.g., a knock-

out/knock-in mouse) would express the transgene of interest as desired at an amount sufficient for the contemplated uses. It is noted that the specification has no working examples indicating that a transgenic mouse properly expressing the transgene of interest at a sufficient level has been produced.

9. Applicants argue that sufficient guidance has been provided in the specification such that one of skill in the art would be able to practice the claimed invention without undue experimentation. Applicants cite the Federal Circuit ruling stating that routine experimentation does not constitute undue experimentation, even if the experimentation is time consuming (See *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1360 (Fed. Cir. 1998). (See p. 9 of the response).

Furthermore, Applicants argue that the application teaches methods well know in the art for making and using the invention as claimed, that the methods for generating the transgene containing constructs and for introducing them into a cell or mouse genome is well known in the art, and that any experimentation required to practice the invention as claimed can be considered routine.

In response, it is acknowledged that the amount of experimentation required is not relevant if the required additional experimentation is routine. It is also acknowledged that the specification teaches a number of different methods for making and testing the transgenic mice encompassed by the claims. However, based on the teachings of the prior art (as previously indicated) the amount of experimentation required to make the transgenic mice that properly express the protein of interest would not be considered routine. As previously indicated, the prior art indicates that it would be unpredictable if the transgenic mouse encompassed by the

claims would properly express the transgene of interest. For instance, regarding the expression of a transgene in a transgenic mouse, Ryan teaches,

> "Disadvantages include differences in transgene copy number and position of integration in the genome. Indeed, there is essentially no control over the number of transgenes that integrate into the genome. Although there is generally no direct correlation between transgene copy number and the level of expression, high-level supraphysiologic expression of transgene is possible, calling into question the physiologic relevance of such a model." (See p. 155, second column); and,
>
> "It is very important to recognize that each of the models described herein have some potential limitations and that no model will perfectly emulate a gene at its normal location in the genome. Moreover, in the end a phenotype observed in these experiments is not only the consequence of the manipulation mode, but the genetic background of the animals being studied. Numerous differences in baseline phenotypes, such as blood pressure and tumor susceptibility, have been reported in different inbred strains of mice. Although most ES cells used in gene targeting are derived from the 129 inbred mouse strain, they are re-implanted into (2578116) blastocysts and then bred with C578176, thus, forming a mixed genetic background. Until 7 to 10 rounds (3-4 years) of successive backcross breading is performed, it is crucial to use non-transgenic littermates as the control animals for any experiment to ensure that the experimental differences do not result from influences of genetic background. This is particularly important when one considers our recent data showing that the 129 strain has a genetic defect in relaxation of the aorta in response to an endothelial-dependent agonists." (See p. 159, first column).

Furthermore, it is also respectfully pointed out (as previously indicated) that Lem teaches knock-out mice that do not express rhodopsin have a degenerative eye disorder wherein the "**rod outer segments failed to form**" (see abstract, emphasis added). The instant claims encompass targeting the transgene of interest into one or both rhodopsin genes, such that the transgene of interest is expressed and targeted to the rod outer segment (ROS) of the eye. It is clear that it would be unpredictable if one of skill in the art could make a transgenic mouse comprising a transgene inserted into one or both rhodopsin genes and expect expression of the transgene such that the transgene is targeted to the ROS, considering that Lem teaches that mice that do not express rhodopsin do not form ROS. It is also pointed out that the development of the eye is a

complicated process involving the precise interaction of many different gene products, and it is unclear how the degenerative disorder of the rhodopsin knock-out mouse would effect the expression and localization of any gene in the eye, without performing additional experimentation.

Applicants also assert that each publication cited in the office action allegedly supporting the assertion that undue experimentation is required is inapplicable to the teachings and guidance provided in the application for how to make and use the invention as claimed (See p. 12-14 of the response). Specifically, Applicants assert that Ryan et al. is inapplicable because the invention is directed to a gene construct or vector, or to a mouse cell or mouse whose endogenous rhodopsin gene is functionally disrupted, and there is no claimed requirement for a phenotype in any of the claims, nor does the use of the claimed construct, vector, cell or mouse require a phenotype. Furthermore, Applicants assert,

> "Manifestation of a phenotype also is not required to practice the invention as claimed without undue experimentation because one purpose of the invention is polypeptide production of the transgene encoded product for subsequent isolation and use. Expression of a polypeptide product in isolatable quantities from a host cell or animal is routine. Failure to correlate a phenotype with the expressed product is inapplicable to practicing the invention as claimed." (See p. 13 of the response).

In response, it is respectfully pointed out that the phenotype that is required is *the proper expression of the transgene in the ROS of the eye of said transgenic mouse* (emphasis added for clarity). Therefore, although no particular phenotype is explicitly claimed, the transgenic mouse MUST properly express the transgene of interest in order for the claimed products to be useful. It is respectfully pointed out that there are no working examples indicating that a transgenic mouse has been made which properly expresses a transgene of interest in the ROS of the eye. Furthermore, the prior art indicates that it is unpredictable that a transgenic mouse, such as one

claimed, would express the transgene of interest as desired. Therefore, proper expression of the instant transgene in isolatable quantities from the contemplated transgenic animal (or a cell therefrom) would not be routine.

With respect to the Lem reference, Applicants argue that Lem indicates that retinal degeneration was initially observed at 90days after birth, and that the rod cells are sufficiently developed prior to the degeneration to achieve ample transgene expression.

In response, it is respectfully pointed out that Lem explicitly teaches that the rhodopsin knock-out mouse has a degenerative eye disorder wherein the "**rod outer segments failed to form**" (see abstract, emphasis added). Therefore, although the mouse *may* be capable of *expressing* the transgene in the early part of its life, it appears to be impossible, absent evidence to the contrary, that the resulting polypeptide would be *localized* to the ROS, considering that the **ROS does not form** in the rhodopsin-null mouse.

With respect to the Holschneider reference, Applicants argue,

> "Holschneider et al. does not support lack of enablement as asserted in the office action because the application teaches the construction of a transgene encoding polypeptide having a ROS target signal flanked by sequences for homologous recombination and operable association with a rod-specific regulatory signal. Therefore, the construct, vector, cell and mouse of the invention claim a transgene under sufficient control that variability in expression is minimized. Moreover, the application teaches convenient methods to confirm transgene expression and targeting after homologous recombination, again minimizing or avoiding variability in expression of the transgene product. Further, Holschneider et al. is concerned with observing changes in phenotype. As described previously, use of the invention as claimed is independent of any change in phenotype or lack of a phenotypic change. Instead, any use based on expression of the transgene can be routinely practiced by making the claimed construct, vector, cell or mouse and determining whether it expresses the transgene product as taught in the application. Accordingly, Holschneider et al. fails to provide an adequate basis for lack of predictability of the claimed invention." (See p. 14).

In response, it is again respectfully pointed out that the phenotype that the transgenic mice must have is the proper expression of the transgene (i.e., the polypeptide of the transgene must be expressed in the eye and the localized to the ROS of the eye). Although the specification teaches methods which may minimize that variability in the expression of the transgene, (such as the use of a construct encoding polypeptide having a ROS target signal wherein the sequence is flanked by sequences for homologous recombination and operable association with a rod-specific regulatory signal) there is no evidence presented that the transgenic mouse would actually express the transgene of interest such that it was targeted to the ROS of the eye of a mouse having decreased or no rhodopsin expression.

Considering the teachings of Lem, Ryan and Holschneider (as previously indicated) it is clear that it would not be a matter of routine experimentation to make a transgenic mouse that expresses a transgene of interest and specifically localizes the encoded polypeptide to the ROS of the eye in said transgenic mouse, considering that the ROS may not develop in the mouse. Furthermore, the amount of experimentation required to be able to make the claimed mouse is considered to be undue because of the problems recognized in the art and discussed herein.

Furthermore, with respect to applicants' assertion that the transgenic mouse could be used for isolating and purifying the transgenic protein, the use of said transgenic mouse for isolating/purifying the transgenic protein is not considered a "real world", because one of skill in the art would not actually make the transgenic animal for the sole purpose of isolating and purifying the transgenic protein from the mouse's eye. Although transgenic animals have been used to produce proteins for isolation/purification, these animals are expensive to make and thus must produce large quantities of the protein in order to be a cost effective option. Additionally,

the transgenic animals typically produce large amounts of proteins in a body fluid of the animal (such as milk, blood, urine, etc). These "bio-reactor" animals can produce very large quantities of transgenic protein, which can be purified from the animal without killing the animal, allowing for the animal to live and produce more of the desired protein. However, even if the claimed mouse could properly express the transgene (which is doubtful considering the evidence presented), the transgenic mouse of the instant invention would not be expected to produce very large amounts of the transgenic protein, and the methods that would be used to isolate/purify the transgenic protein would result in, at least, the loss of eye and maybe the death of the mouse. Therefore, the mouse could not be expected to produce the large amounts of protein typically desired of bio-reactor animals. Furthermore, inexpensive eukaryotic expression systems are well known in the art which can be used to express large quantities of properly modified eukaryotic genes, which can then be isolated and used for antibody production, crystallography assays, etc. Therefore, even if the claimed transgenic mouse could properly produce enough protein for isolation/purification, one of skill in the art would not consider this a "real world" use because it would not result in the isolation of large amount of protein, considering the cost and time required to produce the transgenic mouse and considering that cheaper, effective eukaryotic expressions systems are well known in the art.

Therefore, the instant claims are not enabled and the rejection is not withdrawn.

Conclusion

No claim is allowed.

DAVET NGUYEN
PRIMARY

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on M-F (8:00-5:30), with first Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell, Ph.D.
Art Unit 1635